2

IDENTIFICATION OF CLINICAL AND GENETIC PARAMETERS ASSOCIATED WITH HIDRADENITIS SUPPURATIVA IN INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Background: Hidradenitis suppurativa (HS) has recently been associated with inflammatory bowel disease (IBD). The objective of this study is to investigate the prevalence of HS in IBD and to identify clinical and genetic parameters associated with HS in IBD.

Methods: A questionnaire, validated for HS, was sent to 1969 patients suffering from IBD.

Results: The prevalence of HS in our IBD cohort (1260 participating patients) was significantly higher than in the general population (6.8-10.6 % versus 1-2%). IBD patients with HS were affected by IBD significantly earlier and more often treated with anti-TNF-α therapy and surgical resection compared to IBD without HS. Female gender, smoking, a higher body mass index, and younger age were independent associated parameters for HS. Within cases allelic association analysis was performed for 59 cases (IBD with HS) and 293 controls (IBD without HS). We observed two promising new associations in genomic regions harbouring *ELOVL7* (rsnumber 10057395 $p = 7.15x10^{-5}$, odds ratio = 0.4), and in the intergenic region between *SULT1B1* and *SULT1E1* (rsnumber 2014777 $p = 7.48x^{10-5}$, odds ratio = 2.3).

Conclusion: HS is present in 6.8-10.6 % of IBD patients. Co-morbid HS is associated with an early onset of IBD in which anti-TNF-α therapy and surgical resections are often needed. We identified a suggestive protective association with *ELOVL7* and suggestive risk association with the genes *SULT1B1* and *SULT1E1* for HS, in the context of IBD. These genetic associations need further exploration and replication in additional independent cohorts.

INTRODUCTION

Hidradenitis suppurativa (HS) is a skin condition in apocrine gland bearing regions of the body.[1] The prevalence in Europe is thought to be approximately 1%.[2] Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC).[3] In Western Europe 0.5-1% of the population is diagnosed with IBD.[4] There are numerous similarities between HS and IBD raising the hypothesis for similar pathogenesis. Clinically, HS and CD, are characterized by the formation of sinus tracts and scarring.[1,5] In HS, it has been established that dilatation of the terminal hair follicle leads to rupture of the follicle with leakage of its content into surrounding tissue.[6] The significant associated inflammation is characterized by dysregulation of the immune system.[7,8] In IBD, an inappropriate immune response to commensal bacteria leads to a continuous inflammatory respons.[9] Th-17 cells and TNF-α are considered to be involved in both HS and IBD.[6,10] Moreover it is well known that both chronic inflammatory diseases respond to anti-TNF-α therapy.[5]

CD and HS share similar risk factors. Smoking, being overweight and female gender are the most important risk factors in HS.[11] For CD, smoking cigarettes is considered to be one of the most important risk factors as well.[12,13,14] Remarkably, UC patients have an increased risk of a flare if they quit smoking. Furthermore, high body mass index (BMI) appears to be a risk factor for IBD, mainly for CD.[15]

The role of genetic susceptibility in HS is a subject of ongoing research. Up to 40% of HS patients show a positive family history for the disease. Familial occurrences of HS which follow

an autosomal dominant pattern of inheritance with 100% penetrance have been reported.[11] A candidate locus for HS was indentified at chromosome 1p21.1-1q25.3.[16] However, Ali-Ali et al.[17] could not confirm that HS is linked to loci on chromosome 1p21.1-1q25.3. Mutations in genes encoding the component of gamma-secretase (GS) (presenilin-1, presenilin enhancer-2, and nicastrin) have also been reported.[18] GS is a transmembranous enzyme complex which cleaves the intracellular domain of Notch and thereby enhances intracellular Notch signalling. Notch deficient mice show occlusion of hair follicles, which is the primary event in HS.[19,20] Finally, TNF gene polymorphisms may play a role in susceptibility to HS.[21]

The genetic background is important in the pathogenesis of IBD as well. The nucleotide-binding oligomerization domain containing 2 *(NOD2)* gene was the first identified risk gene for CD.[22] In recent years, large-scale genome-wide association studies have identified 163 independent genomic loci to be associated with IBD.[23] The majority of these 163 susceptibility loci are associated with both CD and UC, suggesting that both diseases have largely overlapping biological mechanisms.

In 2010, van der Zee et al.[5] showed a possible association between HS and IBD in a pilot study. The prevalence of HS was 16% in their IBD population. Recently, van der Zee et al.[5] confirmed a co-incidence in a cohort of 1093 IBD patients.[24] Using anonymous questionnaires, they found a HS prevalence of 23% in this large group of IBD patients. The genetic basis of this association remains unknown.

The objective of this study is to investigate the association between HS and IBD in a large cohort of IBD patients. Moreover, we search for clinical parameters associated with HS in IBD and perform a genetic allelic association analysis to identify genetic variants underlying HS development in IBD.

MATERIALS AND METHODS

Inclusion of patients

All patients diagnosed with IBD in the UMCG before February 2014 were asked to participate in this study. The diagnosis of IBD was made by a gastroenterologist based on clinical, endoscopic and histopathological features. Patients with IBD-unclassified and microscopic colitis were excluded. The participants were requested to fill in a questionnaire, which was sent to their private address. After four weeks, a reminder was sent to the nonrespondents. Anonymously returned questionnaires were excluded. The database was closed after ten weeks. According to Dutch law and the ethical committee a separate informed consent was not needed for sending such a questionnaire. Genotyping was performed in patients who had given written informed consent according to the Dutch Parelsnoer Institute biobanking protocol.

Questionnaire and verification of diagnosis of HS

The questionnaire contained questions about patient characteristics (date of birth, and gender), risk factors (smoking behaviour, family history, length, and weight) and HS. The HS questions were based on a previously validated questionnaire.[25] In addition, prototypical colour pictures of HS lesions in different stages of the disease were added, enabling the patients

to self-assess their presence of HS.
Two sources of ascertaining HS were used. First, the medical records of the patients were checked. We considered the diagnosis of HS valid if it was confirmed by a dermatologist, gastroenterologist or surgeon and if the exact location of the lesions were known. Secondly, in the remaining patients, verification by phone took place. Detailed information was obtained about the presence of inflammation and the location of the skin disorder.

IBD evaluation

The data of all valid respondents was checked on the type of IBD. Moreover, the severity of IBD was assessed by determining the Montreal classification.[26] Additionally, it was established if patients were ever treated with immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate, 6-thioguanine, cyclosporine and tacrolimus) and/or anti-TNF-α therapy and whether they underwent surgical resection in the past.

Statistical analysis

Statistics were performed using IBM SPSS 20.0 software for Windows. Descriptive analyses were applied for all relevant variables. After performing this overall analysis, it was also executed separately for the two major diagnostic categories CD and UC. Group comparison was done by applying independent-samples t-tests or Mann-Whitney U tests for continuous data and chi square tests or Fisher exact tests (if the number of subjects in a cell were less than 5) for dichotomous variables. Association between HS and IBD was examined by estimating the proportion (π) of HS within the study population. Subsequently, the prevalence of HS in the general, healthy population was compared to the prevalence of our IBD study population.
To create an association model, multivariate logistic regression analysis was performed using the presence of HS as the dependant variable. The explanatory variables were gender (male versus female), IBD type (CD versus UC), smoking (current, former or non-smokers), BMI and age. The odds ratios (OR) were calculated and provided by a confidence interval (CI). Finally, the likelihood ratio test was performed. Significance levels were set at $\alpha = 0.05$.

Genetic analysis

We performed genotyping in 355 cases (59 IBD patients with HS and 296 IBD patients without HS) using the Illumina Immunochip (Illumina, Inc., San Diego, CA), which is a custom-made genotyping array designed to densely cover the immune related risk loci with common genetic variants. The Immunochip comprises of ~200.000 SNPs derived from the analysis of genome-wide association studies for twelve immune-mediated diseases.[23]
Raw intensities were normalized using Illumina's Genome Studio program (Illumina, Inc.). Clustering of the intensities and genotype calling was performed using the optiCall clustering program, with a no-calling cutoff set to 0.7.[27] To avoid false positive signals in the genome-wide association studies analysis, a stringent quality control (QC) was performed using PLINK software version 1.07.[28]

Single nucleotide polymorphism QC

Single nucleotide polymorphisms (SNPs) meeting the following criteria were included in the allelic association analysis: being located in the autosomal chromosomes, a Hardy-Weinberg Equilibrium test with a p-value >0.001, a call rate equal or bigger than 98%, and a minor allele frequency greater than 0.05 (minor allele frequency >0.05).

Sample QC

Samples with low genotyping efficiency were removed (call rate < 90%). To identify duplicates or relatedness in the sample dataset, SNPs in high linkage disequilibrium were removed; remaining SNPs were pruned three times for linkage disequilibrium (r^2<0.2), with a window size of 50 SNPs and a step size of 5. A subset of 14618 SNPs was used to calculate the identity-by-descent in PLINK (--genome). Duplicate samples were identified by using an identity value higher than 0.8 (pi-hat>0.8), related samples were identified by using an identity value higher than 0.4 (pi-hat>0.4). After QC, the dataset contained 112974 SNPs, 59 IBD patients with HS and 293 IBD patients without HS.

Genetic allelic association analysis

Within cases allelic association analysis was performed using chi-square test (--assoc) in PLINK. The results of the association were presented in a Manhattan plot using R statistical package (Package 'qqman', Version 0.1.2). In addition, the genotype calling quality for SNPs with the highest p-value were checked manually.

RESULTS

Of the 1969 sent questionnaires, 652 (33%) were not returned. Five patients were excluded due to anonymous submission, 31 questionnaires were returned to sender because the addresses were invalid and 21 patients were excluded for suffering from IBD unclassified (n=13) or microscopic colitis (n = 9) instead of IBD. A total of 1260 (64%) IBD patients replied the questionnaire well-directed and were enrolled.
The baseline characteristics of our patients are demonstrated in Table 1. There is an equal distribution of CD (634) and UC (626) patients.

Prevalence of HS in IBD

Verification of HS was executed in the 246 participants (19.5%) with a positive answer to the HS question. The diagnosis of HS was known from medical dermatology records in 24 cases. The other 222 patients were called; in 110 patients the diagnosis HS was confirmed. In total, 134 of the 1260 to 1969 IBD patients were suffering from HS. The prevalence of validated HS is thus between 6.8 (SD 0.0057 and 95% CI 0.06-0.08) and 10.6% (SD 0.0086 and 95% CI 0.09-0.12). With regard to CD and UC separately, HS was present in 96 of the 634 CD patients and 38 of the 626 UC patients. The 95% CI was 0.124-0.179 (SD 0.0142) for HS in CD and 0.042-0.079 (SD 0.0095) for HS in UC.

	IBD total n (%)
Number of patients	1260
IBD type:	
CD	634 (50.3%)
UC	626 (49.7%)
Gender:	
Female	740 (58.7)
Male	520 (41.3)
Smoking status[a]:	
Nonsmokers	515 (41.1)
Former smokers	500 (39.9)
Current smokers	240 (19.0)
	median (range)
Pack years[a]:	
Current smokers	9.0 (0.03-47.50)
Former smokers	7.5 (0.05-80.00)
	mean (SD)
Age[b] (years)	47.3 (15.8)
BMI (kg/m^2)[a]	25.1 (4.5)

Table 1: Patient characteristics of the IBD population; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis. A) Missing values for smoking status (n = 5), pack years (n = 145) and BMI (n = 23). B) Age was determined at date of closing database (May 21st, 2014).

IBD with HS versus IBD without HS

IBD patients with HS were significantly ($p < 0.001$), more likely to suffer from CD (71.6%) than from UC (28.4%) as shown in Table 2. The prevalence of women (84.3%) was significantly ($p < 0.001$) higher in IBD with HS compared with IBD without HS (55.7%). Participants with HS were found to be significantly younger ($p < 0.001$) than those without HS, 41.8 (12.2) versus 47.9 (16.0) years old respectively. The BMI was significantly higher in the HS group ($p = 0.030$). HS patients were relatively more likely to smoke tobacco compared to patients without HS and less likely to be ex- or non-smokers. However, no significant differences were found in the amount of pack years between currently smoking patients with and without HS ($p = 0.549$).

The Montreal classification shows that significantly more IBD patients with HS had an early onset of IBD compared with the IBD patients without HS. Additionally, late onset of IBD was more frequent in IBD patients without HS. No differences were found in the localization of IBD between IBD with HS and IBD without HS. Stricturing behaviour of CD was more frequent in IBD without HS whereas perianal disease occurred more often in CD patients with HS. Disease extent and severity did not differ between UC with HS and UC without HS. IBD patients with HS were significantly more often treated with anti-TNF-α therapy and had more intestinal resections.

	IBD without HS n = 1126	IBD with HS n = 134	P Value
	n (%)	n (%)	
Type IBD:			
Crohn's disease	538 (47.8)	96 (71.6)	< 0.001
Ulcerative colitis	588 (52.2)	38 (28.4)	< 0.001
Gender:			
Female	627 (55.7)	113 (84.3)	< 0.001
Male	499 (44.3)	21 (15.7)	< 0.001
Smoking status[a]:			
Non-smokers	470 (41.9)	46 (34.3)	0.095
Former smokers	452 (40.3)	48 (35.8)	0.005
Current smokers	199 (17.8)	40 (29.9)	0.001
Montreal classification			
Age of onset			
16 yr or younger	56 (10.6)	8 (11.4)	0.830
17-40 yr	336 (63.5)	55 (78.6)	0.013
Over 40 yr	137 (25.9)	70 (10)	0.003
Localization (CD)			
Terminal Ileum (L1)	107 (36.0)	15 (26.3)	0.158
Colon (L2)	56 (18.9)	13 (22.8)	0.490
Ileocolon (L3)	101 (34.0)	22 (38.6)	0.505
Upper gastrointestinal (L4)	5 (1.7)	0 (0.0)	1.000
L1 +L4	11 (3.7)	3 (5.3)	0.479
L2 +L4	7 (2.4)	1 (1.8)	1.000
L3+L4	10 (3.4)	3 (5.3)	0.447
Behaviour (CD)			
Non stricturing, non penetrating (B1)	123 (38.2)	24 (37.5)	0.916
B1 + perianal (P)	32 (9.9)	16 (25.0)	0.001
Stricturing (B2)	80 (24.8)	6 (9.4)	0.007
B2 + perianal (P)	38 (11.8)	8 (12.5)	0.875
Penetrating (B3)	31 (9.6)	5 (7.8)	0.648
B3 + perianal (P)	18 (5.6)	5 (7.8)	0.493
Extent (UC)			
Proctitis (E1)	41 (16.1)	4 (22.2)	0.511
Left-sided UC (E2)	83 (32.5)	4 (22.2)	0.442
Extensive UC (E3)	131 (51.4)	10 (55.6)	0.731
Severity (UC)			
Remission (S0)	10 (4.2)	0 (0.0)	1.000
Mild (S1)	72 (30.1)	5 (33.3)	0.793
Moderate (S2)	96 (40.2)	5 (33.3)	0.600
Severe (S3)	61 (25.5)	5 (33.3)	0.503
Immunosuppressive agents			
Yes	259 (44.6)	38 (50.0)	0.372
No	322 (55.4)	38 (50.0)	0.372

	IBD without HS n = 1126	IBD with HS n = 134	P Value
Anti-TNF-α therapy			
Yes	111 (19.1)	29 (38.2)	< 0.001
No	470 (80.9)	47 (61.8)	< 0.001
Surgical resection			
Yes	267 (39.1)	52 (58.4)	< 0.001
No	416 (60.9)	37 (41.6)	< 0.001
	median (range)	**median (range)**	
Pack years[a]:			
Current smokers	9.0 (0.03-47.50)	8.0 (0.15-35.00)	0.549
Former smokers	7.4 (0.05-76.00)	8.7 (0.25-80.00)	0.590
Age at onset:			
IBD	-	25.5 (7.00-63.00)	
HS	-	25.0 (6.00-68.00)	
	mean (SD)	**mean (SD)**	
Age[b] (years)	47.9 (16.0)	41.8 (12.2)	< 0.001
BMI (kg/m²)[a]	25.0 (4.4)	26.1 (5.4)	0.030

Table 2: Patient characteristics of IBD without HS versus IBD with HS; IBD: inflammatory bowel disease; HS: hidradenitis suppurativa. A) Missing values for smoking status (n = 5), pack years (n = 145) and BMI (n = 23), Montreal classification (age of onset n=661, localization n=280, behaviour n=248, extent n=353, severity =372), use of immunosuppressive agents and/or anti-TNF-α therapy (n=603) and surgical resection (n=488). B) Age was determined at date of closing database (May 21st, 2014).

CD with HS versus UC with HS

The BMI in CD+HS (25.3 (5.2) kg/m²) was significantly lower (p = 0.009) than in UC+HS (28.0 (5.5) kg/m²). The CD+HS population significantly (p = 0.002) tend to smoke more often, whereas the patients in the UC+HS group are more likely to be former smokers (p < 0.001). Patients with CD+HS demonstrated to have developed their intestinal disease significantly earlier (24.0 (9.00-63.00) years of age) than UC+HS patients (30.0 (7.00-52.00) years of age) with p = 0.018. No significant differences were found for age, gender and onset of HS. All the characteristics described above are shown in Table 3.

Parameters associated with HS in IBD

Multivariable logistic analysis described the relation between HS and its different parameters in an association model, as shown in Table 4. Female gender was the best independent associated parameter for having HS in IBD (OR = 3.494, p < 0.001). In addition, CD patients were more likely than UC patients to have HS (OR = 2.112, p < 0.001). Smoking, a higher BMI and younger age seem to contribute in developing HS as well (OR = 1.910, OR = 1.075, OR = 0.973 respectively). The model including the associated parameters fitted significantly better than without these parameters, with a chi-square value of 94.6 and a p-value < 0.001.

	CD + HS (n = 96)	UC + HS (n = 38)	
	n (%)	**n (%)**	**P value**
Gender:			
Female	84 (87.5)	29 (76.3)	0.108
Male	12 (12.5)	9 (23.7)	0.108
Smoking status[a]:			
Nonsmokers	33 (34.4)	13 (34.2)	0.986
Former smokers	27 (28.1)	21 (55.3)	< 0.001
Current smokers	36 (37.5)	4 (10.5)	0.002
	median (range)	**median (range)**	
Pack years[a]:			
Current smokers	8.0 (0.30-35.00)	9.3 (0.15-33.75)	0.825
Former smokers	6.0 (0.38-80.00)	10.6 (0.25-30.00)	0.191
Age at onset:			
IBD	24.0 (9.00-63.00)	30.0 (7.00-52.00)	0.018
HS	26.0 (6.00-68.00)	23.0 (10.00-65.00)	0.277
	mean (SD)	**mean (SD)**	
Age[b] (years)	41.1 (12.6)	43.6 (10.8)	0.277
BMI (kg/m²)[a]	25.3 (5.2)	28.0 (5.5)	0.009

Table 3: Patient characteristics of CD with HS versus UC with HS; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; HS: hidradenitis suppurativa. A) Missing values for smoking status (n = 5), pack years (n = 145) and BMI (n = 23). B) Age was determined at date of closing database (May 21st, 2014).

	β	P-value	Odds Ratio	95% CI
Gender	1.251	< 0.001	3.494	2.138-5.712
IBD type	0.748	< 0.001	2.112	1.389-3.213
Smoking behaviour	0.647	0.010	1.910	1.167-3.126
BMI (kg/m²)	0.073	< 0.001	1.075	1.035-1.118
Age (years)	-0.028	< 0.001	0.973	0.959-0.987

Table 4: Multivariate logistic regression of risk factors for hidradenitis suppurativa; IBD: inflammatory bowel disease.

Genetic association analysis

We performed a within cases allelic association analysis for 59 IBD patients with HS and 293 IBD patients without HS. We did not identify any signals at genome wide significance level (p-value < 1.0×10^{-8}). Two suggestive genetic association signals were observed on chromosome 4 and 5 (Figure 1, Table 5). The first signal on chromosome 4, rs2014777 (p-value of 7.5×10^{-5}; OR 2.3) resides in an intergenic region between *SULT1B1* and *SULT1E1*. The genetic association signal on chromosome 5, rs10057395 (p-value 7.2×10^{-5}; OR 0.4) is in a genomic region harbouring *ELOVL7*. Both SNPs passed our QC measures (including manual cluster plot inspection) and the regions show additional SNPs showing signals of suggestive evidence for association (Figure 2a and Figure 2b).

Chromosome	Position	SNP	Gene	OR	P-value
4	70706332	rs2014777	*SULT1B1, SULT1E1*	2.25	$7.48x10^{-5}$
5	60124551	rs10057395	*ELOVL7*	0.43	$7.15x10^{-5}$

Table 5: Genes with the highest association for HS in IBD; Position is relative to human reference genome GRCh37; HS: hidradenitis suppurativa; IBD: inflammatory bowel disease; SNP, single nucleotide polymorphism; OR, odds ratio.

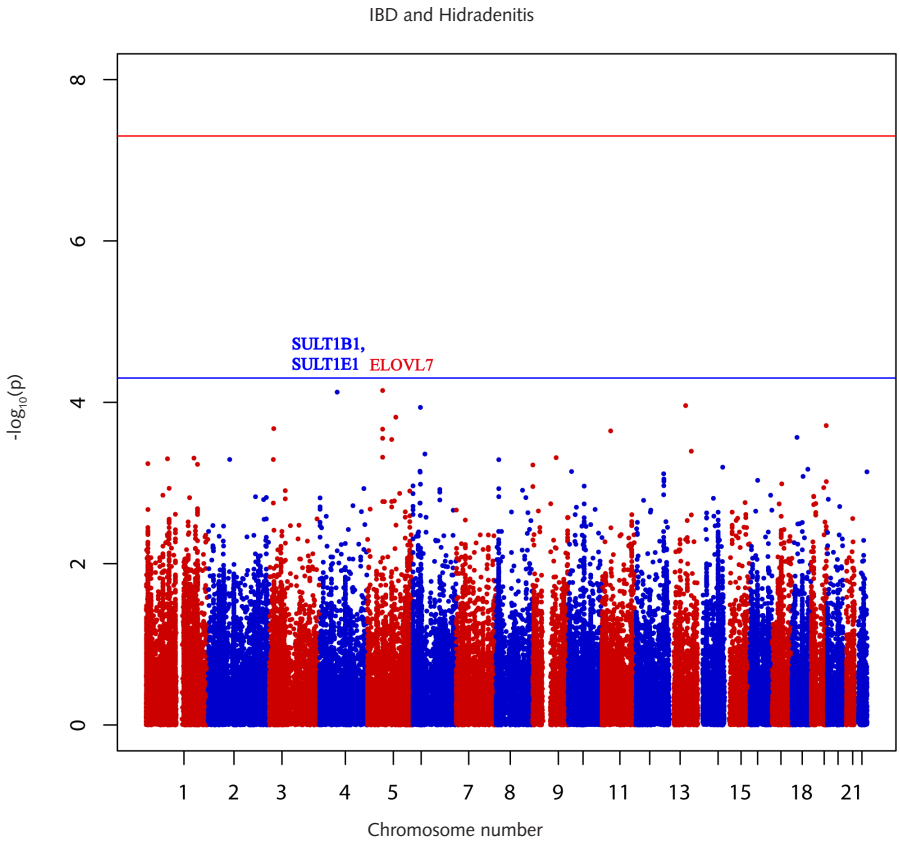

Figure 1: Manhattan plot of association tests of all single nucleotide polymorphism that passed stringent QC; The red horizontal line indicates the threshold for genome-wide significance (p-value of 1.0x10-8). The blue horizontal line indicates a p-value of 1.0x10-5.

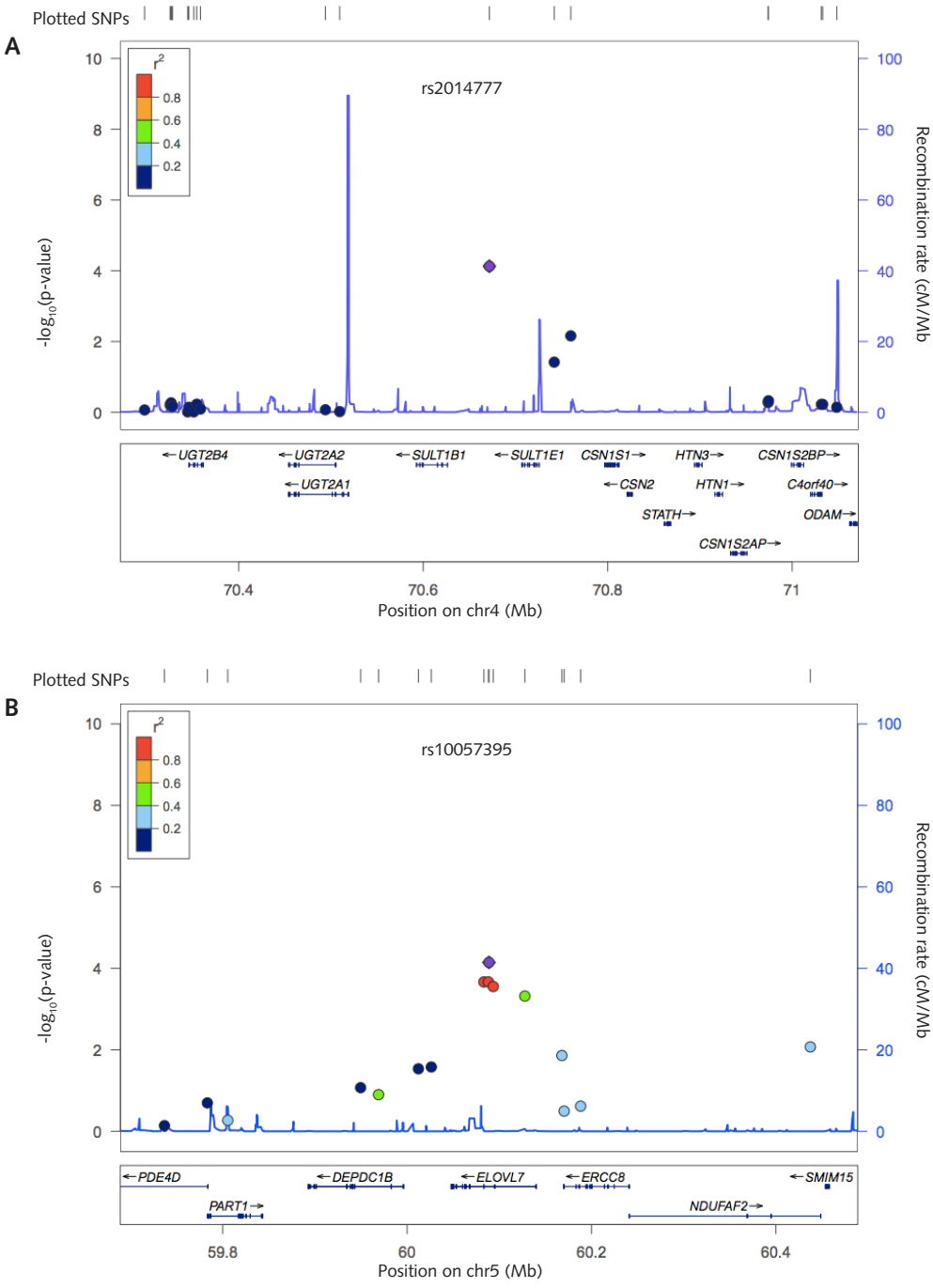

Figure 2: Regional association plots of the two suggestive genetic association signals (purple triangles).; Filled in circles are genotyped SNP's from the Immunochip. The colour illustrates linkage disequilibrium with the associated SNP (2a: rs2014777 2b: rs10057395).

DISCUSSION

The first goal of this study was to investigate the association between HS and IBD. The prevalence of HS in our IBD population is 6.8-10.6%, significantly higher than the prevalence in the general population (1%) confirming the association of the two diseases.[2] Moreover, we demonstrate that HS is also associated with CD and UC separately. In 2010 and 2014, van der Zee et al.[5,24] found a conspicuous higher prevalence of HS in IBD patients compared to our prevalence (16% and 23%, versus 6.8-10.6% in our study). We believe our data is more accurate because of the verification of HS. Questionnaires used for the investigation of HS prevalence are only validated in the general population.[25] Because in IBD, especially in CD, enterocutaneous fisteling and perianal skin changes frequently occur, patients can confuse this with HS.

The distribution of IBD type within the HS patients was practically similar to the previous study, with 71.6% CD patients in our population and 71.0% in van der Zee et al.[24] The higher prevalence of HS in CD suggests that the association between IBD and HS predominantly exists due to CD. This might be explained by the fact that genetic influence is stronger in CD than in UC.[29]

The influence of HS on IBD severity has up until now never been described. Our results indicate that co-morbid HS is associated with an early onset of IBD in which anti-TNF-α therapy and surgical resections are often needed. Moreover, we confirmed the finding of frequent perianal IBD in HS patients as previously described by Yadaz et al.[30]

When comparing CD+HS with UC+HS, CD+HS patients seem to be more often current smokers. The same smoking status was found in the study of van der Zee et al.[24] The difference in mean BMI between CD+HS and UC+HS was higher in our patients, in favour of CD, compared to the previous study, where mean BMI was nearly equal in the two IBD types.[24] A high BMI in CD could be an independent risk factor.

Striking differences can be found when comparison is made between HS patients in our IBD population and HS patients in the general population called regular HS (RHS). The RHS group investigated by Sartorius et al.[31] in a large Swedish population turned out to be heavier (28.3 kg/m^2) than our IBD+HS group (26.1 kg/m^2). The most reasonable explanation is that IBD patients more often suffer from malnutrition secondary to the intestinal disease.[32] On the contrary, in HS, overweight is a well-known risk factor and the BMI of patients is predominantly too high, even though dermatologists strictly insist on patients losing weight.[1,31] The prevalence of smoking is also remarkably higher in RHS patients (70.0%) compared with IBD+HS patients (29.9%).[31,33] HS patients with IBD (35.8%) are more likely than those without IBD (15.0%) to have quit smoking.[31] The explanation for the difference in smoking behaviour might be that the majority of IBD+HS patients suffer from CD. Cessation of smoking improves the course in CD patients, contrary to UC patients, where cessation even may cause flares of the disease.[34] However, in RHS the influence of quitting smoking on disease course is unknown and stopping seems to make no difference.[35]

The parameters associated with HS in our IBD population correspond to the risk factors in RHS: female gender, smoking and obesity. The prevalence of currently smoking and heavy HS

patients is much higher in the general population than in the IBD population, as mentioned above. Additionally, our data shows that younger IBD patients are more likely to have HS than older participants. This corresponds with previous research, demonstrating that HS mainly initiates in the early twenties.[1]

We identified suggestive signals for genetic association for HS in IBD at two genomic loci harbouring the genes *ELOVL7, SULT1B1* and *SULT1E1. SULT1B1* and *SULT1E1* belong to the sulfotransferase family, encoding enzymes that catalyze the sulfate conjugation of hormones, drugs, neurotransmitters and xenobiotic compounds.[36] The suggestive signal for *SULT1E1* might have a relevant link with HS for several reasons. First of all, *SULT1E1* encodes for an enzyme which is involved in oestrogen homeostasis.[37] Oestrogens also seem to play a role in HS. Exacerbations of HS occur frequently during relatively hypo-oestrogenic states. It is therefore hypothesized that oestrogens exert a protective effect for the disease.[38] Another reason why *SULT1E1* might be linked to HS is that it is expressed in abdominal subcutaneous tissue in obese males and females (BMI > 30 kg/m^2). Adiposity is an important risk factor for HS.[11] Moreover, Ahima et al.[37] found oestrogen expression in abdominal adipose tissue in association with expression of TNF-α. TNF-α plays an important role in the disease pathogenesis of CD and HS and both diseases respond well to anti-TNF-α therapy. The gene *ELOVL7* encodes a long-chain fatty acid elongase and has no obvious link with HS.[39]

Little is known in literature about the genetic background of HS in IBD patients. Gao et al.[16] identified a candidate locus for HS at chromosome 1p21.1-1q25.3. However, we could not confirm this association in our IBD cohort. Although the current cohort was underpowered to identify genetic association signals at genome-wide significance level, we observed suggestive evidence for association at two genomic loci harbouring potential candidate genes *ELOVL7, SULT1B1* and *SULT1E1*. To confirm these genetic associations for HS in IBD, additional independent cohorts need to be analyzed.

In conclusion, this is the first study reporting the association between IBD and HS in such a large cohort. Our study demonstrates the importance of verification of HS in patients recruited from validated questionnaires. In IBD patients, co-morbid HS is associated with an early onset of IBD in which anti-TNF-α therapy and surgical resections are often needed. The development of HS in IBD is associated with female gender, CD, smoking, higher BMI and younger age. Gastroenterologists should therefore pay special attention to this group of patients as they are at risk of developing HS.

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40